MIND MINUTE

An update provided by the Coordinated Care Group of the Alzheimer's State Plan

DEMENTIA MEDICATIONS UPDATE

Remember: All FDA-approved therapies for Alzheimer disease are symptomatic treatments only. No currently available drugs have been shown to be neuroprotective or to halt cognitive and functional decline.

Why is this important? Cognitive benefits achieved by the use of medications for Alzheimer disease are generally modest at best, and side effects are not uncommon. Realistic expectations need to be discussed with patients and their families at the initiation of treatment, and follow-up for assessment of benefits and side effects as well as ongoing discussions of goals of care are necessary. If a decision is made to discontinue pharmacologic treatment, the drug should be tapered before discontinuation, and restarted if the patient worsens when the drug is stopped.

Cholinesterase Inhibitors (ChIs)

There are currently three ChIs approved by the FDA for treatment of Alzheimer disease: donepezil, galantamine, and rivastigmine. These drugs slow the breakdown of the neurotransmitter acetylcholine which is associated with learning and memory. All three medications have similar side effect profiles which are dose-dependent and therefore require a **slow titration** in order to maximize benefit while avoiding adverse events. Start low and go slow! One study suggests that even lower than the standard 5 mg starting dose of donepezil was associated with fewer adverse events in older women.

The most common adverse events for ChIs are nausea, loss of appetite, diarrhea, insomnia, headaches, dizziness, orthostasis and nightmares. More serious adverse events are felt to be related to increased vagal tone and include bradycardia, hypotension and syncope. **Avoid use of ChIs in patients with baseline bradycardia or cardiac conduction delays.**

To date there are no data showing significant differences in efficacy among these three drugs. There may be small differences in tolerability. In one trial donepezil was more likely to be titrated to the maximum dose. Two other studies found lower discontinuation rates for donepezil and galantamine.

Remember: There is no good evidence supporting use of ChIs in patients with mild cognitive impairment. It does not appear to prevent progression from MCI to dementia.

Remember: Only donepezil has FDA approval for use in patients with **all stages** of Alzheimer disease. Galantamine and rivastigmine are approved for mild to moderate disease only.

Remember: Evidence does **not** support use of dosages higher than 10 mg of donepezil, and there are increased adverse effects at higher doses.

What about use of ChIs for treatment of other types of dementia? It has become increasingly apparent that many patients diagnosed with Alzheimer disease actually have mixed dementia, especially Alzheimer/vascular pathology combination. It may therefore be reasonable to offer a trial of ChIs for patients with vascular dementia. There is also some evidence for use of ChIs for patients with Parkinson disease dementia, with rivastigmine carrying an FDA approval for this. **ChIs should not be used for frontotemporal dementia or dementia associated with Huntington disease or multiple sclerosis.**

Memantine

There is one NMDA antagonist which is FDA approved for **moderate to severe** Alzheimer disease only: memantine. This drug is felt to have neuroprotective effects by mediating excitotoxic effects of glutamate. Cognitive measures, behavior, and ADLs have been shown to have **minimal improvement** in patients with Alzheimer disease. It has been shown to be safe for use in combination with donepezil in moderate to late stage Alzheimer disease. It may be used alone if donepezil is not tolerated. It is not recommended for use in any other type of dementia.

The most common adverse effects of memantine are constipation, dizziness, and headache. Again, slow titration is recommended in order to minimize adverse effects. Target doses are adjusted in severe renal impairment.

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Summary: Typical Pharmacological Treatment Course

Mild Alzheimer disease: Start donepezil 2.5 to 5 mg nightly for women, 5 mg nightly for men and titrate every 6 weeks to maximum dose of 10 mg daily. Monitor for GI side effects and bradycardia. Assess response after 6 months on target or highest tolerated dose. Consider tapering over time if no initial response or if continued decline despite maximum treatment doses.

Moderate to severe Alzheimer disease: Consider addition of memantine extended-release 7 mg daily titrating weekly to target dose of 28 mg daily. Monitor for constipation, dizziness, and headache. If patients are stable on target 10 mg dose of donepezil, Namzeric® may be used, alternatively. Monitor for adverse effects. Assess for response after 6 months on target dose.
Consider tapering over time if continued decline despite maximum treatment doses, or if side effects are observed.

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Dr. Kim Tarver is an Assistant Professor of Medicine in the Division of Geriatrics at the University of Mississippi Medical Center where she trained and became board certified in Internal Medicine and Geriatrics. Dr. Tarver also serves as Director of MIND Center Clinical Services. She has over 20 years' experience in clinical practice and teaching in the area of Geriatrics.

Dr. Tarver has additional certificate training in psychotherapy from the Institute of Contemporary Psychoanalysis in Los Angeles, California. She also sees patients in the MIND Center Clinic at UMMC and divides her clinical time between dementia evaluations, primary care of geriatric patients and psychotherapy with older adults.

Contact Information: If you would like more information on this topic or would like to suggest future topics for the MIND MINUTE publication, please contact The MIND Center at mindcenter@umc.edu or 601-815-4237.

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Summary Treatment Chart

Generic	Brand	FDA Approval	Starting Dose / Titration	Contraindications / Dose adjustments	Side Effects
Donepezil	Aricept®	Mild, Moderate and severe AD	Women: 2.5 -5mg Men: 5 mg Titrate every 6 weeks to 10 mg as tolerated	Baseline bradycardia, cardiac conduction delay	Nausea, loss of appetite, diarrhea, insomnia, headaches, dizziness, orthostasis and nightmares
Galantamine	Razadyne®	Mild to moderate AD	8 mg extended-release daily with food Titrate every 4 weeks to 24 mg extended-release daily with food as tolerated	Baseline bradycardia, cardiac conduction delay, ESRD, severe hepatic impairment	Nausea, loss of appetite, diarrhea, insomnia, headaches, dizziness, orthostasis and nightmares
Rivastigmine	Exelon®	Mild to moderate AD Mild to moderate dementia with PD	4.6 mg/24 hr. patch daily Titrate every 4 weeks to 13.3 mg/24 hr. max dose as tolerated	Baseline bradycardia, cardiac conduction delay, severe hepatic impairment Dose adjustment for mild –mod. hepatic impairment and body wt. < 50 kg. Use only lowest dose.	Nausea, loss of appetite, diarrhea, insomnia, headaches, dizziness, orthostasis and nightmares
Memantine	Namenda®	Moderate to severe AD	5 mg/d x 1 week 5 mg BID x 1 wk. 10 mg/d x 1 week Then 10 mg BID	Target dose 5 mg BID in severe renal impairment. (CrCl 5 to 29 mL/min)	Constipation, dizziness, and headache
Memantine + Donepezil	Namzaric®	Moderate to severe AD	For pts stable on donepezil 10 mg, start 7 mg/10 mg/d in evening. Titrate weekly to target dose 28 mg/10 mg/d.	Target dose reduced to 14/10 mg daily for severe renal impairment. (CrCl 5 to 29 mL/min)	Nausea, loss of appetite, diarrhea, insomnia, headaches, dizziness, orthostasis and nightmares, constipation, dizziness, and headache

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